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Arterial Thrombosis, GM-CSF, and the Lupus Anticoagulant

To the Editor: Recombinant colony stimulating factors such as granulocyte–macrophage colony stimulating factor (GM-CSF) have been advocated for use in severe drug-induced neutropenia. Side effects include both arterial and venous thrombosis, although almost all reported cases have occurred in cancer patients on chemotherapy. We report a case of arterial thrombosis in a patient with clozapine-induced neutropenia being treated with GM-CSF, who had the potentially additive prothrombotic risk factor of a drug-induced lupus anticoagulant (LAC).

A 30-year-old polynesian male with longstanding manic depression was admitted 8 weeks after starting clozapine, his neutrophil count having fallen to 0.1×10^9/L. He had been treated in previous years with fluphenazine and chlorpromazine. He was a smoker with no family history of thrombosis. Treatment with oral ciprofloxacin and fluconazole antimicrobial prophylaxis, and GM-CSF (300 μg/day subcutaneously) was started. On day 3 of treatment he suddenly developed a dense left-sided hemiplegia. CT scan showed a large cerebral infarction in the right middle cerebral artery territory. Doppler studies showed complete occlusion of right internal and external carotid arteries with thrombus. Activated partial thromboplastin time was prolonged at 39 sec (control 36 sec), and prothrombin time was normal. LAC testing (by Kaolin Clotting Time and Dilute Russell's Viper Venom Test) was positive. Screening for anticardiolipin antibodies, protein S, protein C, and antithrombin III deficiencies, as well as activated protein C resistance was negative. Fibrinogen was initially elevated at 8.5 g/L (later falling to 6.0 g/L). ANA was detectable at a titre of 1:40; double-stranded DNA was negative.

GM-CSF was replaced with G-CSF, and the patient was warfarinized.

DISCUSSION

There have been many case reports of thrombotic events in cancer patients on chemotherapy receiving GM-CSF for neutropenia. A recent meta-analysis strongly suggested (but did not prove) that GM-CSF, but less so granulocyte colony stimulating factor (G-CSF), was associated with thrombotic risk [1]. There are no reports of thrombotic events in drug-induced neutropenia treated with GM-CSF that we are aware of. Potential mechanisms of thrombosis include increased tissue factor expression on macrophages [2], enhanced expression of adhesion molecules on neutrophils (with resultant binding to vascular endothelium resulting in damage) [1], and increased platelet aggregation (reported with G-CSF) [3].

Given that the majority of reported cases had additional thrombotic risk factors it is of interest that our patient was also discovered to have a (presumed) drug-induced lupus anticoagulant (LAC). Chlorpromazine has been associated with the LAC in up to 50% of treated patients and a case of clozapine-induced LAC was recently reported in this journal [4]. The risk of thrombosis in these patients is controversial, and while some authors are convinced that it is increased [5] the overall incidence appears to be low. It may, however, have contributed to our patient's catastrophic thrombotic event.

Given that G-CSF appears to have a lesser prothrombotic tendency than GM-CSF, we would advocate the use of the former where potential thrombotic risk factors already exist.

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REFERENCES

1. Barbui T, Finazzi G, Grassi A, Marchioli R. Thrombosis in cancer patients treated with haematopoietic growth factors: a meta analysis. On behalf of the Subcommitee on Haemostasis and Malignancy of the Scientific and Standardisation Committee of the ISTH. Thrombosis Haemostasis 1996;75(2):368–371.
2. Edwards RL, Rickles FR. The role of leucocytes in the activation of blood coagulation. Semin Haematol 1992;29:202–212.
3. Kuriowa M, Okanura T, Kanaji T, Okamura S, Harada M, Niho Y. Effects of granulocyte colony-stimulating factor on the haemostatic system in healthy volunteers. Int J Hematol 1996;63(4):311–316.
4. Kanjolia A, Valigorsky JM, Josion-Pasion ML. Clozaril-induced lupus anticoagulant. Am J Hematol 1997;54:345–346.
5. Bick RL, Baker WF. Antiphospholipid and thrombosis syndromes. Semin Thrombosis Haemostasis 1994;20:3–15.